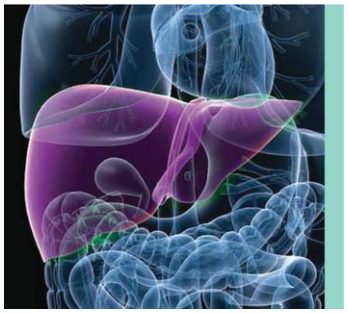

Managing the Patient With Acute Liver Failure

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Acute liver failure (ALF) is a rare condition characterized by new and rapidly evolving hepatic dysfunction associated with neurological dysfunction and coagulopathy. It is more frequent in young individuals, and its causes vary geographically, with impact on both clinical course and outcomes. Throughout the last few decades, ALF outcomes have been improving in the context of the optimized overall management. However, its present morbidity and mortality are still of concern.

DEFINITION AND EPIDEMIOLOGY

ALF definition has evolved and currently includes the following features: international normalized ratio (INR) $\geq$ 1.5, neurological dysfunction with any degree of hepatic encephalopathy (HE), no preexisting cirrhosis, and disease course $\leq$26 weeks. ALF causes are summarized in Table 1 and corresponding investigations in Table 2. ALF outcomes have been improving in recent decades. In a multicenter registry from the United States in 1998 to 2010, ALF 2-year survival rate has been reported as 92% for liver transplant (LT) recipients, 90% for acetaminophen overdose spontaneous survivors, and 76% for nonacetaminophen spontaneous survivors.[1] This positive trend in ALF survival has been associated with the earlier recognition of this condition, improvement of the intensive care unit management, and developments in emergent LT.

Abbreviations: ALFSG, Acute Liver Failure Study Group; ALT, alanine aminotransferase; AKI, acute kidney injury; ALF, acute liver failure; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBc, hepatitis B virus core antibody; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HE, hepatic encephalopathy; HELLP, hemolysis, elevated liver enzymes, and low platelets; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HVP, high-volume plasmapheresis; Ig, immunoglobulin; INR, international normalized ratio; LDH, lactate dehydrogenase; LT, liver transplant; MARS, molecular adsorbent recirculating system; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine; SIRS, systemic inflammatory response syndrome; VZV, varicella zoster virus.

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TABLE 1. ACUTE LIVER FAILURE CAUSATIVE FACTORS

- Viruses
  - Hepatitis A, B, D, or E viruses
  - Cytomegalovirus
  - Epstein-Barr virus
  - Herpes simplex virus
  - Varicella zoster virus
  - Parvovirus
- Drug-induced liver injury
  - Acetaminophen
  - Nonacetaminophen (e.g., isoniazid, phenytoin, valproate, propylthiouracil, nitrofurantoin)
  - Recreational drugs (e.g., cocaine, MDMA)
- Autoimmune hepatitis
- Ischemic/congestive hepatitis
- Budd-Chiari syndrome
- Wilson's disease
- *Amanita phalloides*
- Pregnancy (e.g., acute fatty liver of pregnancy, HELLP syndrome)
- Heat stroke
- Malignant infiltration
- Seronegative (indeterminate)

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and low platelets; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine.

TABLE 2. INITIAL LABORATORY TESVTS FOR ACUTE LIVER INJURY OR ACUTE LIVER FAILURE

Assessment	Test
Severity (serum)	Arterial blood gas
	Arterial lactate
	Arterial ammonia
	Hemoglobin, leucocytes, platelets
	INR, aPTT, fibrinogen, factor V
	AST, ALT, bilirubin, albumin, alkaline phosphatase, LDH, amylase
	Creatinine, urea, sodium, chloride, potassium, calcium, magnesium, phosphorus, creatine kinase
Etiology (serum or urine)	HAV IgM, HBsAg, HBc IgM, anti-HCV, anti-HEV, CMV IgM, EBV IgM, HSV IgM, VZV IgM, anti-HIV
	Ceruloplasmin, copper
	Anti-nuclear antibody, anti-smooth muscle antibody, Igs
	Paracetamol, toxicology screen
	Blood type
	Pregnancy test (females)

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBc, hepatitis B virus core antibody; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; Ig, immunoglobulin; LDH, lactate dehydrogenase; VZV, varicella zoster virus.

MANAGEMENT OF THE PATIENT WITH ACUTE LIVER FAILURE

A summary of organ failure complications of ALF is provided in Table 3.

Coagulopathy

In ALF, overall hemostasis as measured by thromboelastography has been shown to be normal by several compensatory mechanisms, even in patients with markedly elevated INR.[2] In the absence of active bleeding or invasive procedure, it is not advisable to correct the INR with fresh frozen plasma, because clinically significant blood loss is rare and correction obscures trends in the INR, an important marker of prognosis. A platelet count greater than $50 \times 10^{9/L}$ and fibrinogen greater than 1.5 g/L have been demonstrated to correlate with normal thrombin generation and, indirectly, bleeding.[3]

Infection

ALF risk for immunoparesis increases susceptibility to infection, which may preclude emergent LT. Therefore, surveillance for infection (including chest radiography and periodic cultures of sputum, urine, and blood) should be undertaken, while maintaining a low threshold for starting antimicrobial therapy. Prophylactic antimicrobials have not been proven to improve 21-day survival in ALF.[4]

Hemodynamics

Patients with ALF typically present a hyperdynamic circulation characterized by high cardiac output and low peripheral vascular resistance, a pattern resembling that of sepsis. For patients who continue to have hypotension despite volume repletion, noradrenaline is the preferred vasopressor, with or without adjunctive use of vasopressin or its analogues.[5] Echocardiography or invasive hemodynamic monitoring (e.g., PiCCO, Swan-Ganz catheter) should be used to assess cardiac function and help titrate decisions on the doses of fluids and/or vasopressors. Relative adrenal insufficiency may be present, and the use of steroids has been associated with a decrease in noradrenaline dose and overall mortality.

TABLE 3. ORGAN COMPLICATIONS OF ACUTE LIVER FAILURE

Organ Failure	Pathophysiology
Liver	Hyperlactatemia: decreased lactate clearance
	Hyperammonemia: decreased ammonia clearance
	Coagulopathy: decreased synthesis of procoagulant and anticoagulant factors
	Hypoglycemia: decreased gluconeogenesis
	Portal hypertension: may develop especially in subacute disease
Brain	HE: circulating inflammatory mediators and hyperammonemia
	Cerebral edema: inflammatory mediators from microglial cells and glutamine accumulation in astrocytes
Cardiovascular	Hypotension or shock, especially if sepsis superimposes
Lungs	Acute lung injury or acute respiratory distress syndrome: SIRS, sepsis, and/or fluid overload
Kidneys	AKI: SIRS, sepsis, and/or hypovolemia
Pancreas	Acute pancreatitis: SIRS and/or drug toxicity (e.g., paracetamol)

Abbreviation: SIRS, systemic inflammatory response syndrome.

Acute Kidney Injury

Acute kidney injury (AKI) may develop in up to 70% of patients with ALF and has been associated with worse overall survival.[6] Classic indications for renal replacement therapy initiation also apply, including severe acidosis, hyperkalemia, anuria, and/or fluid overload. Further indications may include removal of toxic substances (e.g., ammonia), difficult-to-treat hyponatremia, or difficult-to-treat hyperthermia. Continuous renal replacement therapy has been proposed to safer for patients with ALF given the risk for aggravating hypotension and cerebral edema.[7]

Cerebral Edema and Intracranial Hypertension

In ALF, astrocyte swelling may result in cytotoxic brain edema, which may culminate in tonsillar herniation and death. Frequent neurological examination (including pupils) and the use of transcranial Doppler are simple strategies to monitor for signs of cerebral edema and intracranial pressure. On the contrary, computed tomographic findings compatible with intracranial hypertension often present too late in the course of this condition. Invasive monitoring of intracranial pressure has not been shown to improve these patients' hospital survival.[8] Nevertheless, it is still not clear whether patients with the highest risk for cerebral edema and intracranial hypertension (e.g., ammonia level $>$ 150 mmol/L, vasopressors requirement, or renal replacement therapy requirement) may benefit from such monitoring capacity.[9] Interventions aimed at prevention of intracranial hypertension include: (1) place head of the bed higher than 30 degrees; (2) use propofol sedation if requiring mechanical ventilation; (3) treat fever (prophylactic hypothermia has not been demonstrated to mitigate intracranial hypertension)[10]; (4) aim for a mean arterial pressure $\geq$75 mm Hg and a cerebral perfusion pressure greater than 50 mm Hg (if using invasive intracranial pressure monitoring); (5) consider using renal replacement therapy; and (6) aim for a serum sodium concentration of 145 to 155 mmol/L with hypertonic saline (3%-30% infusion) for prophylaxis in patients with grade III-IV HE.

Extracorporeal Liver Support Systems

Two extracorporeal liver support systems have been studied in ALF with randomized controlled trials: molecular adsorbent recirculating system (MARS) and high-volume plasmapheresis (HVP). MARS, where blood is dialyzed against a dialysate with albumin, has not been proven to improve 6-month survival in ALF.[11] HVP has been shown to significantly improve hospital survival, especially for patients with contraindications for LT.[12]

LIVER TRANSPLANTATION AND PROGNOSTICATION

LT is the only definitive treatment for patients with ALF. Overall survival after LT has been reported to be lower for patients with ALF in comparison with patients with cirrhosis until 1 year after transplant, but it tends to be similar beyond this period. Cadaveric donor LT has been the norm in ALF, but living-donor transplant has been performed in some large-volume centers with acceptable outcomes. Auxiliary transplantation (partial graft as temporary support for native liver regeneration) has shown reasonable outcomes. Stratifying patients based on their risk for death without LT is crucial to prioritize them for transplantation. King's College criteria have been used worldwide for this purpose (Table 4). A recent meta-analysis has revealed its prognostic ability in comparison with the Model for End-Stage Liver Disease

TABLE 4. KING'S COLLEGE CRITERIA AND ACUTE LIVER FAILURE STUDY GROUP PROGNOSTIC INDEX IN ACUTE LIVER FAILURE

Acetaminophen-Related ALF	Non-Acetaminophen-Related ALF
King's College Criteria[14]	
A. Single criterion:	A. Single criterion:
pH <7.30 or lactate >3.0 mmol/L after adequate fluid resuscitation	INR >6.5
B. Three criteria:	B. Three of five criteria:
Grade III-IV (West-Haven) HE	Age <10 or >40 years
INR >6.5	Time from jaundice to coma >7 days
Creatinine >3.4mg/dL	INR >3.5
	Bilirubin >17mg/dL
	Unfavorable etiology: drug-induced liver injury, Wilson's disease, or seronegative liver injury
ALFSG Prognostic Index[13]	
Grade III-IV (West-Haven) HE (yes or no)	
Favorable etiology	
Acetaminophen, pregnancy, ischemia, hepatitis A	
All others unfavorable	
Vasopressor use (yes or no)	
Serum bilirubin	
INR	

score: for paracetamol-related ALF, sensitivities were 58% and 80%, respectively, and specificities were 89% and 53%, respectively; for nonparacetamol causes, sensitivities were 58% and 76%, respectively, and specificities were 74% and 73%, respectively. Therefore, King's College criteria remain highly specific for paracetamol-related ALF, but less accurate for nonparacetamol causative factors. More recently, the US Acute Liver Failure Study Group (ALFSG) prognostic index showed good performance characteristics (C-statistic 0.84, specificity 95%) in 1974 patients in the ALFSG registry.[13] This is demonstrated in Table 4 and is a commercially available app.

CONCLUSIONS

ALF diagnostic and therapeutic strategies have evolved and are now associated with improved outcomes. New advances in basic and clinical research may potentiate even more such outcomes. Despite this, early patient referral to an LT center, timely intensive care unit therapy, and a comprehensive multidisciplinary strategy in risk stratification and selection for LT will continue to be fundamental steps for a successful approach.

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REFERENCES

1) Fontana RJ, Ellerbe C, Durkalski VE, Rangnekar A, Reddy RK, Stravitz T, et al. Two-year outcomes in initial survivors with acute liver failure: results from a prospective, multicentre study. Liver Int 2015;35:370-380.

2) Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol 2012;56:129-136.

3) Habib M, Roberts LN, Patel RK, Wendon J, Bernal W, Arya R. Evidence of rebalanced coagulation in acute liver injury and acute liver failure as measured by thrombin generation. Liver Int 2014;34:672-678.

4) Karvellas CJ, Cavazos J, Battenhouse H, Durkalski V, Balko J, Sanders C, et al. Effects of antimicrobial prophylaxis and blood stream infections in patients with acute liver failure: a retrospective cohort study. Clin Gastroenterol Hepatol 2014;12:1942-1949.e1941.

5) Eefsen M, Dethloff T, Frederiksen HJ, Hauerberg J, Hansen BA, Larsen FS. Comparison of terlipressin and noradrenalin on cerebral perfusion, intracranial pressure and cerebral extracellular concentrations of lactate and pyruvate in patients with acute liver failure in need of inotropic support. J Hepatol 2007;47:381-386.

6) Tujios SR, Hynan LS, Vazquez MA, Larson AM, Seremba E, Sanders CM, et al. Risk factors and outcomes of acute kidney injury in patients with acute liver failure. Clin Gastroenterol Hepatol 2015;13:352-359.

7) Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit Care Med 1993;21:328-338.

8) Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM, et al. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med 2014;42:1157-1167.

9) Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007;46:1844-1852.

10) Karvellas CJ, Todd Stravitz R, Battenhouse H, Lee WM, Schilsky ML, US Acute Liver Failure Study Group. Therapeutic hypothermia in

acute liver failure: a multicenter retrospective cohort analysis. Liver Transpl 2015;21:4-12.

11) Saliba F, Camus C, Durand F, Mathurin P, Letierce A, Delafosse B, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med 2013;159:522-531.

12) Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol 2016;64: 69-78.

13) Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a model to predict transplant-free survival of patients with acute liver failure. Clin Gastroenterol Hepatol 2016;14:1199-1206.e2.

14) O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97: 439-445.